UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

[SEQ CHAPTER \h \r 1]**MEMORANDUM**

Date: June 18, 2019

SUBJECT: **Mecoprop (MCPP)**: Tier I Update Review of Human Incidents and Epidemiology for Draft Risk Assessment

PC Codes: 031501, 031503, 031519, 031520, 031563, 031564, 119046, 129046
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Summary and Conclusions

Mecoprop (MCPP) incidents were previously reviewed in 2014 (S. Recore and E. Evans, D417595, 02/04/14). At that time, there were no incidents reported for MCPP as a single

chemical only, but there is a high absolute number of incidents reported involving MCPP with another active ingredient. Although the majority of these incidents were of low severity, some high severity outcomes are reported in the IDS database. Based on the absolute number of incidents and the few high severity outcomes that are reported, it was concluded that these incident data may warrant further analysis in the preliminary risk assessment phase of Registration Review.

In the current IDS analysis from January 1, 2014 to April 11, 2019, there were 128 incidents reported that involved the active ingredient MCPP to Main IDS. There were 830 MCPP incidents reported to Aggregate IDS. A query of SENSOR-Pesticides from 2011-2015 identified 77 cases involving MCPP. All the MCPP incidents reported to IDS and SENSOR-Pesticides involved multiple active ingredients. It is important to note that since most of these reported incidents involve more than one active ingredient (i.e. MCPP and another active ingredient), the incidents that were reported were not necessarily attributable to MCPP. The number of MCPP incidents reported continues to be moderately high; however, most incidents were low in severity (IDS (87%) and SENSOR-Pesticides (88%)) and a trend of MCPP incidents reported to IDS overtime, from 2009 to 2018, shows that MCPP incidents have declined approximately 70%, from a peak of 371 incidents reported in 2010 to only 113 reported in 2018. Based on the incident data reported to both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time.

The Agricultural Health Study (AHS) is a federally-funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), Centers for Disease Control and Prevention National Institute of Occupational Safety and Health (CDC/NIOSH), and the United States Environmental Protection Agency (EPA). MCPP is included in the AHS, and, there is no evidence at this time to conclude that a clear associative or causal relationship exists between MCPP exposure and the carcinogenic and non-carcinogenic health outcomes assessed in the two AHS studies reported here. The Agency will continue to monitor the epidemiology data, and -- if a concern is triggered -- additional analysis will be conducted.

Detailed Review

I. ACTION REQUESTED

MCPP is being considered under the FQPA-mandated Registration Review program established to review, on a 15-year cycle, pesticides for which a Re-registration Eligibility Decision has been made. HED's RAB VII has requested that the Toxicology and Epidemiology Branch conduct a Tier I Update review summary of recent incident data from IDS and SENSOR as per standard protocol under the Agency's Registration Review Program. One component of the Agency's Registration Review Program is consideration of human incident data. In conjunction with a human health risk assessment based on other data sources, such human incident data can assist the Agency in better defining and characterizing the risk of pesticides/pesticide products.

It is important to remember that reports of adverse health effects allegedly due to a specific pesticide exposure (*i.e.*, an "incident") are largely self-reported and therefore, generally speaking, neither exposure to a pesticide or reported symptom (or the connection between the two) is validated or otherwise confirmed. Typically, causation cannot be determined based on incident data, and such data should be interpreted with caution. Nonetheless, incident information can be an important source of feedback to the Agency: incidents of severe outcome, or a suggested pattern or trend among less severe incidents, can signal the Agency to further investigate a particular chemical or product. Epidemiology studies can also be useful and relate the risk of disease, *e.g.*, cancer, and exposure to an agent such as a pesticide product in the general population or specific sub-groups like pesticide applicators.

II. BACKGROUND

MCPP compounds are plant growth regulators that are part of the chlorophenoxy group of herbicides. MCPP is used in combination with other herbicides for postemergence broadleaf weed and brush control. It is used primarily on turf (i.e. lawns and golf courses) and sod farms with smaller quantities used on non-turf areas such as rights-of way.

For this evaluation, both OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases were consulted for pesticide incident data on the active ingredient MCPP (PC Codes: 031501, 031503, 031519, 031520, 031563, 031564, 119046, 129046). The purpose of the database search is to identify potential patterns in the frequency and severity of the health effects attributed to MCPP exposure.

III. RESULTS/DISCUSSION

a. IDS (Incident Data System)

OPP's IDS includes reports of alleged human health incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6(a)(2) reports from registrants, other federal and state health and environmental agencies, and individual consumers. Since 1992, OPP has compiled these reports in IDS. IDS contains reports from

across the U.S. and most incidents have all relevant product information recorded. Reports submitted to the IDS represent anecdotal reports or allegations only, unless otherwise stated in the report.

IDS records incidents in one of two modules: Main IDS and Aggregate IDS:

- Main IDS generally contains incidents resulting in higher severity outcomes and provides more detail with regard to case specifics.[1] This system stores incident data for death, major and moderate incidents, and it includes information about the location, date and nature of the incident. Main IDS incidents involving only one pesticide are considered to provide more certain information about the potential effects of exposure from the pesticide.

- Aggregate IDS contains incidents resulting in less severe human incidents (minor, unknown, or no effects outcomes). These are reported by registrants only as counts in what are aggregate summaries.

For the Main IDS for the five years from January 1, 2014 to April 11, 2019, there were 128 incidents reported that involved the active ingredient MCPP.[2] All of these MCPP incidents involved multiple active ingredients. There was one fatality reported and one incident was classified as major severity. Upon further review, these incidents do not appear to be related to the product used. The fatality occurred in 2018. An adult female, who was 10 weeks pregnant, had a miscarriage after coming within three feet of the product which had spilled on the floor of the shed a week earlier. The major severity case occurred in 2014. A 35-year-old male applied the product to his yard. He experienced lightheadedness, nausea and had a stroke. He was taken to the hospital and the doctor did not believe the stoke was related to the product.

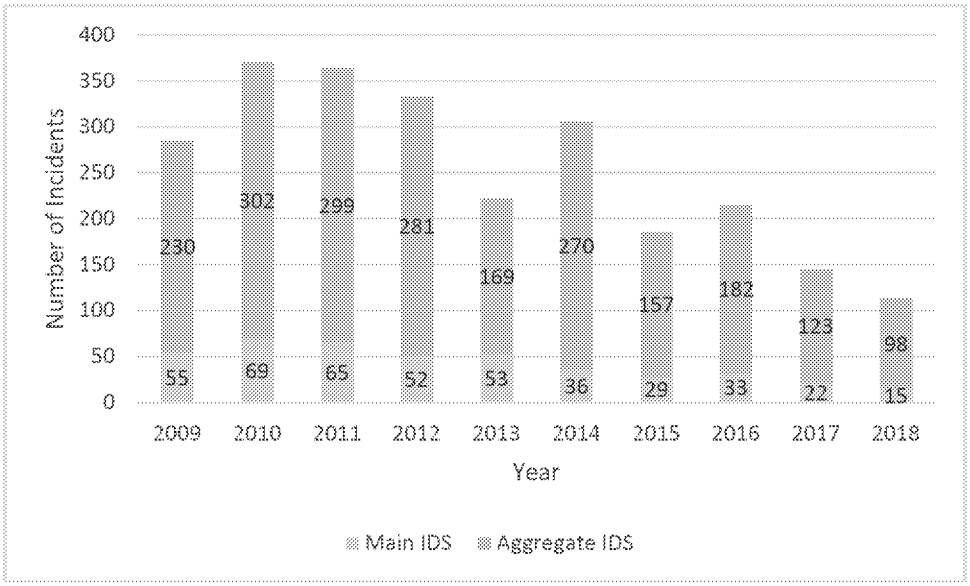
One hundred twenty five incidents were classified as moderate severity and one incident was classified as having no or unknown effects.

For Aggregate IDS for the five years from January 1, 2014 to April 11, 2019, there were 830 incidents reported involving MCPP. Twelve incidents had no or unknown effects and 818 were classified as minor severity.

The incident trend from 2009 to 2018 was reviewed (Figure 1).[3] The incidents appear to be declining approximately 70%, from a peak of 371 incidents reported in 2010 to only 113 reported in 2018.

[1] Occasionally, low severity incidents are self-reported by the consumer directly to Main IDS.
[2] There were also four incidents that occurred in England and 3 in Canada. Foreign incidents are not reviewed in detail because of the potential differences in the exposure patterns, use practices, and product formulation.
[3] This includes all incident from this MCPP incident memo and the previous incident memo (S. Recore and E. Evans, D417595, 02/04/14)

Figure 1. MCPP Incidents Reported to IDS from 2009 to 2018



b. SENSOR-Pesticides

The Center for Disease Control's National Institute for Occupational Safety and Health (CDC/NIOSH) manages a pesticide surveillance program and database entitled the Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides.[4] All cases must report at least two adverse health effects. Evidence for each case is evaluated for its causal relationship between exposure and illness based on the NIOSH case classification index.[5] Using standardized protocol and case definitions, SENSOR-Pesticides state coordinators, operating out of the state's department of health, receive state pesticide incident reports from local sources, then follow up with case sources to get incident scenario to obtain medical records and verify exposure scenario information.[6] This database includes pesticide illness case reports from multiple states from 1998-2015.[7]

A query of SENSOR-Pesticides from 2011-2015 identified a total of 77 cases involving MCPP. All cases involved multiple active ingredients. Nine cases were moderate in severity and 68 cases were low in severity. Off-target movement of the pesticide was an exposure factor reported in 38 of the 77 MCPP cases.

Symptoms frequently reported among the 77 cases included: abdominal pain, vomiting, diarrhea, nausea, dermal irritation, headache, rash, skin irritation, dizziness, and eye irritation.

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[4] SENSOR-Pesticides webpage: [HYPERLINK "http://www.cdc.gov/niosh/topics/pesticides/overview.html"].

[5] [HYPERLINK "https://www.cdc.gov/niosh/topics/pesticides/pdfs/casedef.pdf"]

[6] [HYPERLINK "https://www.cdc.gov/niosh/topics/pesticides/pdfs/pest-sevindexv6.pdf"]

[7] Currently participating states are: California, Florida, Illinois, Louisiana, Michigan, Nebraska, New Mexico, North Carolina, Oregon, Texas and Washington. The participating states for a given year vary depending on state and federal funding for pesticide surveillance.

c. Agricultural Health Study (AHS)

The AHS is a federally-funded prospective cohort study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's National Institute of Occupational Safety and Health (NIOSH), and the US EPA. The AHS participant cohort includes more than 89,000 licensed commercial and private pesticide applicators and their spouses from Iowa and North Carolina. Enrollment occurred from 1993 – 1997, and data collection is ongoing. The AHS maintains a list of publications resulting from AHS studies.[8]

In creating this Tier 1 memorandum, EPA reviewed the AHS publications listed on the AHS publication website. As of June 2019, two AHS publications investigated associations between MCPP exposure and reported estimates of health effects, one involving non-Hodgkin lymphoid malignancies and the other wheeze. These studies are summarized below.[9]

Non-Hodgkin lymphoid malignancies

Leon et al. (2019) examined the association between pesticide exposure in farmers and non-Hodgkin lymphoid malignancies (NHL) in a pooled analysis of data from three agricultural cohort studies, including AHS, as part of the AGRICOH consortium. The AGRICOH is an international consortium of agricultural cohort studies that pool data to investigate health outcomes. The three cohorts included in this meta-analysis investigating effects of pesticide exposure on NHL were: (i) the AHS (data from commercial applicators excluded) of the United States; (ii) the Agriculture and Cancer (AGRICAN) cohort of France; and (iii) the Cancer in the Norwegian Agricultural Population (CNAP) cohort of residents of Norway. The three prospective cohorts assessed all incident cases of NHL and subtypes self-reported during follow-up (the date of enrollment for AHS and AGRICAN participants and 1993 for CNAP, the earliest year of follow-up) and through periodic data linkages to cancer and mortality registries. Specifically for the AHS, this meta-analysis includes data from the AHS private applicators/farmers (commercial applicators were excluded), with registry linkages until December 31, 2010 (North Carolina) and December 30, 2011 (Iowa). Pesticide exposure was assessed through self-report of ever exposure to pesticide active-ingredients (AHS) and self-report of crops cultivated combined with country-specific crop-exposure matrices (AGRICAN and CNAP) to derive estimates of ever exposure to individual pesticides including MCPP. Cohort members were linked with appropriate cancer and mortality registries and the U.S National Death Index (AHS and CNAP only) to identify cases of NHL and NHL subtypes. Cox proportional hazard regression models were used to estimate the association between ever-use of MCPP and incident NHL and NHL subtypes for each cohort, with never exposure as the referent. The AHS cohort specific regression model was adjusted for sex, state of residence, livestock (animal production), and pesticides terbufos, lindane, DDT, permethrin, dicamba, parathion, and

[8] Agricultural Health Study: Publications https://aghealth.nih.gov/news/publications.html

[9] In evaluating and reporting on the AHS studies, for odds ratios (ORs), risk ratios (RRs), and hazard ratios (HRs), the confidence interval (CI) acted as a proxy for significance testing, with CIs that do not contain the null value (OR / RR / HR = 1.00) considered significant.

carbaryl.[10] Resulting individual cohort estimates for MCPP were then combined using random effects meta-analysis. Among the 316,270 farmers and farm workers included in the combined study population, 2,430 were cases of NHL (493 cases were participants of the AHS cohort). Among the 493 reported NHL cases within the AHS cohort included in the present study (n=51,167), 123 (24.9%) were diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), 113 (22.9%) cases were diagnosed with diffuse large B-cell lymphoma (DLBCL), 96 (19.5%) cases were diagnosed with multiple myeloma/plasma-cell leukemia (MM), and 64 (13.0%) were diagnosed with follicular lymphoma (FL). The AHS cohort-specific risk estimates for the association between MCPP exposure and NHL overall and NHL subtypes were not reported. The authors reported no evidence of a positive association was reported for MCPP ever exposure and overall NHL (i.e., all subtypes considered together) (OR = 0.94; 95% CI: 0.61, 1.46, n = 776 exposed cases) in the meta-analysis based on all three cohorts. For NHL subtypes, no evidence of a significant positive association was reported for the association between MCPP ever-exposure and any NHL subtype ($0.82 < HR < 1.06$; all CIs encompassed the null value of 1.00, with 59 – 175 cancer cases per type of cancer, with AHS not included in this subtype analysis). The meta-analyses for MCPP ever exposure and any of the NHL subtypes were based on the AGRICAN and CNAP cohorts only (AHS data was not included).

Wheeze

Hoppin et al. (2016) examined the association between allergic and non-allergic wheeze and MCPP exposure among male farmers through a cross-sectional analysis of data from the AHS study population. The study population consisted of male participants in the AHS who completed the 2005 – 2010 follow-up interview detailing current pesticide usage (n = 22,134) and reported symptoms of wheeze. Wheeze was defined as at least one episode of wheeze or whistling in the chest in the past year and a physician-diagnosis of hay fever for allergic wheeze, and at least one episode of wheeze or whistling in the chest in the past year without a diagnosis of hay fever for non-allergic wheeze. Survey information was used to assess current use (since the last AHS interview), past use (not used since the last AHS interview), and never use of MCPP and frequency and duration of use. A polytomous logistic regression was used to determine the association between wheeze and pesticide exposure, with allergic and non-allergic wheeze investigated separately. Models were adjusted for body mass index (BMI), current asthma, age, smoking, and state, as well as for days applying pesticides and days driving diesel tractors. Among the 1,310 *allergic* wheeze cases, <1% reported current use of MCPP, and among the 3,939 *non-allergic* wheeze cases, 1% reported current use of MCPP. Among the 16,885 control subjects, <1% reported current use of MCPP. No evidence of a positive association was reported for the association between current MCPP use and *allergic* wheeze (OR = 0.89; 95% CI: 0.35, 2.29) based on ever use and no evidence of a significant positive association was reported for *non-allergic* wheeze (OR = 1.33; 95% CI: 0.83, 2.14) based on ever exposure since the last interview.

[10] Each cohort Cox regression was adjusted for slightly different covariates: AGRICAN: sex, livestock, retirement status, number of selected types of crops for which pesticide treatment personally applied. CNAP: sex, livestock, dichlorvos, aldicarb, lindane, DDT, deltamethrin, mancozeb, linuron, glyphosate. AHS: sex, state, livestock, terbufos, lindane, DDT, permethrin, dicamba, parathion, carbaryl.

The authors also conducted exposure-response modeling based on cumulative days of use, dividing the distribution of current users of MCPP into tertiles based on frequency of use to better evaluate any exposure-response and the high end of the exposure distribution. The following exposure categories for frequency of use of MCPP were created for the exposure-response analysis: past use; 1 day of use since the last AHS interview; 2 days of use since the last AHS interview; and 3 – 60 days of use since the last AHS interview. Never use served as the referent category for the analysis. For the exposure-response analysis for *allergic* wheeze, each exposure category contained n<5 cases per exposure category and as such authors did not report risk estimates for any exposure categories with fewer than five cases. For the exposure-response analysis between MCPP and *non-allergic* wheeze, no evidence of significant positive association was reported for any exposure category ($1.24 \leq OR \leq 2.07$; all CIs encompassed the null value of 1.00 for all exposure categories, with 4 – 12 cases per exposure category). The mid-exposure level (2 days of use since the last AHS interview) was not reported because n<5 cases (n=4) in this exposure category. An elevated but non-significant OR was reported for the high exposure category for *non-allergic* wheeze (3-60 days of use since the last AHS interview: OR = 2.07; 95% CI: 1.00, 4.29, with n=11 cases). The authors did not report a p-trend statistic for the exposure-response analysis for non-allergic wheeze and MCPP; however, inspection of the ORs associated with each category suggests an exposure-response trend may exist. However, sample sizes in each exposure category for *non-allergic* wheeze are small making the results less reliable.

Epidemiology Conclusion

In creating this Tier I Update memorandum, EPA reviewed the AHS publications listed on the AHS publication website. Two published studies investigating the potential association between MCPP exposure and human health effects among the AHS study cohort were reviewed. There is no evidence to suggest a clear associative or causal relationship between MCPP and the NHL and wheeze health outcomes investigated in the AHS studies reported here.[HYPERLINK "file:///C:/Users/AAldridg/Documents/Isoxaflutole/epi%20summaries_isoxaflutole.docx" \l "_ftn2" \h][11]

One study, Leon et al. (2019), included AHS data in a larger multi-cohort meta-analysis and reported no evidence of a significant positive association between MCPP exposure and both NHL overall and NHL subtypes among male farmers. And one AHS study (Hoppin et al. 2016) reported no evidence of a significant positive association for allergic wheeze and no evidence of a significant positive association for non-allergic wheeze. The Agency will continue to monitor the epidemiology data, and -- if a concern is triggered -- additional analysis will be conducted.

IV. CONCLUSION

[11] Causality as defined by the Bradford-Hill considerations: strength of association, consistency of evidence, specificity of the association, temporality, dose-response, biological plausibility, and coherence with established knowledge. Via Hill, Austin Bradford. "The environment and disease: association or causation?." Proceedings of the Royal society of Medicine 58.5 (1965): 295.

MCPP incidents were previously reviewed in 2014 (S. Recore and E. Evans, D417595, 02/04/14). Based on the absolute number of incidents reported in the previous analysis, TEB concluded that MCPP incident data may warrant further analysis in the preliminary risk assessment phase of Registration Review. In the current review, the MCPP incidents reported to both IDS and SENSOR-Pesticides continue to involve multiple active ingredients. It is important to note that since most of these reported incidents involve more than one active ingredient (i.e., MCPP and another active ingredient), the incidents that were reported were not necessarily attributable to MCPP. The number of MCPP incidents reported continues to be moderately high; however, most incidents were low in severity (IDS (87%) and SENSOR-Pesticides (88%)) and a trend of MCPP incidents reported to IDS over time, from 2009 to 2018, shows that MCPP incidents have declined approximately 70%, from a peak of 371 incidents reported in 2010 to only 113 reported in 2018. Based on the incident data reported to both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time.

With respect to the epidemiology studies reviewed, there is no evidence at this time to conclude that a clear associative or causal relationship exists between MCPP exposure and the NHL and wheeze health outcomes assessed in the AHS studies reported here. [12] The Agency will continue to monitor the epidemiology data and -- if a concern is triggered -- additional analysis will be conducted.

Citations:

1. Hoppin, J. A., Umbach, D. M., Long, S., London, S. J., Henneberger, P. K., Blair, A., Alavanja, M., Beane Freeman, L.E., Sandler, D. P. (2016). Pesticides are associated with allergic and non-allergic wheeze among male farmers. *Environmental Health Perspectives*, *125*(4), 535-543.

2. Leon, M. E., Schinasi, L. H., Lebailly, P., Beane Freeman, L. E., Nordby, K. C., Ferro, G., Monnereau, A., Brouwer, M., Tual, S., Baldi, I., Kjaerheim, K. (2019). Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA: a pooled analysis from the AGRICOH consortium. *International Journal of Epidemiology*.

[12] Causality as defined by the Bradford Hill considerations: strength of association, consistency of evidence, specificity of the association, temporality, dose-response, biological plausibility, and coherence with established knowledge. Via Hill, Austin Bradford. "The environment and disease: association or causation?." Proceedings of the Royal Society of Medicine 58.5 (1965): 295.

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